UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,590	09/09/1999	ELIZABETH MOYER	00211-US-NEW	2967

21971 7590 12/08/2005

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,590	MOYER ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *29-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/09/05.* and 113005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 09/13/05 in response to the non-final Office Action mailed 07/21/05.

Status of Claims

2) Claims 1, 4, 6, 7, 16, 18-20, 29 and 40 have been amended via the amendment filed 09/13/05.

Claims 1-53 are pending.

Claims 1-28 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statement

5) Acknowledgment is made of Applicants' information disclosure statement filed on 09/09/2005 and 11/30/05. The information referred to therein has been considered and a signed copy of the same is attached to this Office Action.

Personal Interview dated 30 September 2005

6) Applicants' remarks made in their response filed 09/13/05 with regard to the personal interview held on 09/30/05 have been noted. The potential rejoinder of the method claims in accordance with *In re Ochiai* was indicated when the product claims are found to be in condition for allowance. In response to Applicants' argument that the formulation disclosed in the applied prior art references contain high concentrations of purified botulinum toxin which do not constitute therapeutic concentrations, Applicants were reminded that the currently claimed formulation is not a 'therapeutic' composition. The lack of 'therapeutic' indications/limitations

in the draft claims was specifically brought to Applicants' attention. The specific suggestions that were given during the interview were accompanied by a caution that the specification must provide descriptive support for such limitations and enablement for such a formulation.

Claim Interpretation

7) The instant application does not contain a limiting or non-limiting definition for the term 'buffered saline' or 'saline'. The term 'buffered saline' or 'saline' does not appear in Example 1 and Table 1. The single mention of a 'buffered saline' appears at line 20 of page 7 of the specification, which is *not* described as 'pharmaceutically acceptable'. While there is a description herein of 'physiological buffer', there is no recitation of a 'physiological' saline or 'isotonic' saline. A concentration of 5.8 mg/mL of NaCl as recited at line 15 of page 20 of the specification yields 0.58% NaCl which is not equivalent to isotonic saline (0.9%), nor physiologic saline (0.85%). In the absence of a specific definition in the instant specification, a limitation is to be given a reasonably broad interpretation. See MPEP 2111. The court has held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, 'the PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification'. The Office's interpretation of the limitation 'saline' is based on the broadest Dictionary definition. For example, the *Webster's II New Riverside University Dictionary* (The Riverside Publishing Company, page 1032, 1984) defines the term 'saline' as being 'related to, or containing salt' (see page 1032). It should be noted further that the term 'salt' is not limited to NaCl alone, but encompasses any salt other than NaCl. Therefore, the interpretation of the term 'saline' does not have to be restricted or limited to 'containing NaCl'.

Rejection(s) Withdrawn

8) The rejection of claims 6 and 7 made in paragraph 9(a) of the Office Action mailed 07/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

9) The rejection of claims 19 and 20 made in paragraph 9(b) of the Office Action mailed 07/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

10) The rejection of claims 1-8 and 16-21 made in paragraph 11 of the Office Action mailed 07/21/05 under 35 U.S.C § 102(b) as being anticipated by Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

11) The rejection of claims 1-8 and 16-21 made in paragraph 12 of the Office Action mailed 07/21/05 under 35 U.S.C § 102(b) as being anticipated by Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

12) The rejection of claims 1-8, 12-21 and 25-28 made in paragraph 14 of the Office Action mailed 07/21/05 under 35 U.S.C § 102(b) as being anticipated by Schantz *et al.* (EP 0 593 176 A2, already of record) ('176), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

13) The rejection of claims 14, 15, 27 and 28 made in paragraph 15 of the Office Action mailed 07/21/05 under 35 U.S.C § 103(a) as being unpatentable over Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record), or Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980) or Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS) as applied to claim 1 or claim 16 and further in view of Schantz *et al.* (*Microbiol. Rev.* 56: 80-89, 1992) (Schantz *et al.*, 1992, already of record), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

14) The rejection of claims 9-11 and 22-24 made in paragraph 16 of the Office Action mailed 07/21/05 under 35 U.S.C § 103(a) as being unpatentable over Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record), or Saprykina *et al.* (*Zh. Mikrobiol. Epidemiol. Immunobiol.* 9: 86-91, 1980) as applied to claim 8 or claim 21 above and further in view of Melling *et al.* (*Eye* 2: 16-23, 1988 – Applicants' IDS), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

15) The rejection of claims 1-8 and 16-21 made in paragraph 13 of the Office Action mailed 07/21/05 under 35 U.S.C § 102(b) as being anticipated by Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS), is withdrawn in light of Applicants' amendment to the claims and/or the base claims. A modified rejection is set forth below.

16) The rejection of claims 12, 13, 25 and 26 made in paragraph 17 of the Office Action mailed 07/21/05 under 35 U.S.C § 103(a) as being unpatentable over Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974 – Applicants' IDS) as applied to claim 8 or claim 21 above, is withdrawn in light of Applicants' amendment to the claims and/or the base claims. A modified rejection is set forth below.

New Rejection(s) Based on Applicants' Amendment

The new rejections set forth below are necessitated by Applicants' amendments to the claims. Applicants' arguments with respect to the previous art rejections have been considered, but are moot in view of the withdrawal of those rejections and the new/modified rejections set forth below.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

17) Claims 1, 16 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The base claims 1 and 16 now include the added recitation 'stabilized' liquid pharmaceutical botulinum toxin formulation .... 'capable of being' stable .... Applicants do not point to a specific part of the specification that provides descriptive support for the new limitation. There appears to be no support in the instant specification, as originally filed, for the limitation newly added to claims 1 and 16. The term 'stabilized' liquid pharmaceutical botulinum toxin formulation does not appear in the specification, as originally filed. Claims 1 and 16 further include the limitations: "a pharmaceutically acceptable buffered saline capable of providing a buffered pH range 'to the formulation' between pH 5 and pH 6" at the temperature recited. Applicants point to lines 24-28 on page 3; lines 15-16 on page 4; lines 18-21 on page 7; lines 3-11

and 13-15 on page 14; page 21; and Table 1 of the specification for alleged support. However, these parts of the specification do not provide support for any 'pharmaceutically acceptable' 'buffered saline' that is capable of providing a buffered pH range 'to the formulation' between pH 5 and pH 6. Instead, these parts of the specification describe a 'buffer' that is capable of providing a buffered pH range between about pH 5 and pH 6. The 'buffered saline' described at line 20 of page 7 of the specification is not described as having a pH of between 5 and 6, or is capable of providing a buffered pH range to the formulation between pH 5 and pH 6. Pages 20 and 21 of the specification describe a pH 5.6 'succinate buffer' containing specific amounts of NaCl and human albumin. Therefore, the above-identified new limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitations, or to remove the new matter from the claim(s).

18) Claims 6 and 19 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 6 and 19 now include the added limitation: said 'buffered saline' has a pK in the range of pH 4.5-6.5. Applicants do not point to a specific part of the specification that provides descriptive support for the new limitation. A review of the specification indicates that there is no support in the instant specification, as originally filed, for a 'buffered saline' having a pK in the range of pH 4.5-6.5. Therefore, the above-identified new limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claim(s).

19) Claims 7 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 7 and 20 now include the added limitation: said 'buffered saline' 'selected from the group consisting of phosphate buffer, phosphate-citrate buffer, and succinate buffer'. Applicants do not point to a specific part of the specification that provides descriptive support for the new limitation. A review of the specification indicates that while there is descriptive support for phosphate buffer, phosphate-citrate buffer, and succinate buffer in the second full paragraph of page 4, there is no support in the instant specification, as originally filed, for a 'buffered saline' that is phosphate buffer, phosphate-citrate buffer, or succinate buffer. Therefore, the above-identified new limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

20) Claims 1-14 and 16-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a stable liquid pharmaceutical formulation comprising 5000 $\pm$ 1000U/ml of a purified type B botulinum toxin and a pH 5.6 succinate buffer containing 5.8 mg/ml NaCl and supplemented with0.5 mg/mL human serum albumin, wherein the liquid formulation is capable of being stable as a liquid when stored for at least one year at a temperature of 5 degrees centigrade, or for at least six months at a temperature of 25 degrees centigrade, does not reasonably provide enablement for a stabilized liquid pharmaceutical formulation comprising a therapeutic concentration suitable for human use of any purified

botulinum toxin and a 'buffered saline' (with or without gelatin or human serum albumin) capable of providing a buffered pH range to the formulation of between 5 and 6 and having a pK in the range of pH 4.5 – 6.5, wherein the formulation is capable of being stable as a liquid for at least one year at the recited pH and temperature ranges for at least one year or at least about 6 months, as claimed currently.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a stabilized liquid pharmaceutical botulinum toxin formulation for therapeutic use in humans comprising a therapeutic concentration of a purified botulinum toxin and a pharmaceutically acceptable buffered saline that is capable of providing a buffered pH range to the formulation of between pH 5 and 6 wherein the formulation is capable of being stable as a liquid when stored at the recited temperature ranges of between 0 and 10 $\pm$ 10%, or between 10 and 30 $\pm$ 10% degrees centigrade for a period of at least one year and at least about 6 months respectively. Encompassed in the scope of the claims are stabilized liquid pharmaceutical formulations of purified type A, C1, C2, D, E, F or G botulinum toxin contained in any 'buffered saline' capable of providing a pH range between 5 and 6 to the formulation at a temperature of about 0-10 or about 10-30 degrees centigrade. The precise composition of the 'buffered saline' including the concentration(s) of the buffer component(s) and of 'saline' are not disclosed, let alone their pK. Furthermore, the limitation 'a therapeutic concentration' appears to encompass at least the concentration ranges of the toxin recited in the dependent claims 9, 11-13, 22 and 24-26, i.e., 100-20,000 U/ml $\pm$ 10%; 1000-5000 U/ml; 20-2000 U/ml; and 100-1000 U/ml. The 'stabilized' formulation of claims 1-13

and 16-26 is not required to comprise an excipient protein such as serum albumin, human serum albumin, or gelatin, whereas the stabilized formulation of claim 14 and 27 comprises any generic excipient protein, including a protein other than gelatin and serum albumin. The state of the art at the time of the invention indicates that botulinum toxins in solvent or liquid form varied in their stability based on the type of buffer used, the pH, the temperature used for storage, and the presence or absence of nontoxin proteins. A review of the relevant art shows that the low concentrations, i.e., therapeutic concentrations, of a botulinum toxin are very unstable. For instance, Schantz *et al.* (*Perspect. Biol. Med.* 40 (3) Spring 317-327, 1997) taught the following (see paragraph bridging pages 322 and 323) [Emphasis added]:

> The formulation and stabilization of the toxin for dispensing to physicians and subsequent injection into patients required much care and research. For this purpose, the toxin had to be diluted 10,000- to 20,000-fold from a stable concentration of 2 or more mg per ml to an unstable concentration of 100 U or ~33 ng per ml before being dispensed to physicians. **At these low concentrations, the toxin is very unstable**, and **rapid detoxification occurs unless another protein is added at the time of dilution**. A proposed medium for compounding of botulinum toxin contained human serum albumin at 5 mg per ml to stabilize the toxin, in a solution containing 9 mg of sodium chloride to assure good solubility of the toxin.

In the instant application, a concentration of a 5000 $\pm$ 1000U/ml of a purified type B botulinum toxin has been shown to be stable as a liquid pharmaceutical formulation in a buffer that is referred to under Example 1 as pH 5.6 'succinate buffer' (as opposed to 'succinate buffered saline'). This succinate buffer contains 5.8 mg/mL NaCl and 0.5 mg/ml of human serum albumin. A concentration of 5.8 mg/mL of NaCl yields 0.58% NaCl which neither amounts to isotonic saline (0.9%), nor physiologic saline (0.85%). Example 2 and Table 2 show that a concentration of about 2500 Units/ml of the type B botulinum toxin remains stable for at least one year at one particular temperature of 5°C and at a pH of 5.6 in this succinate buffer. Table 3 of the specification demonstrates that the liquid botulinum type B toxin formulation with a mean potency of 1579 U/ml was stable for at least 6 months in the above-mentioned 'succinate buffer' at a single temperature of 25°C and a pH of 5.6. Human serum albumin is a *required* component of this stable formulation. There is absolutely no showing within the instant specification that any pharmaceutically acceptable buffered saline that does not contain human serum albumin or gelatin is indeed capable of stabilizing the formulation comprising a therapeutic concentration of a purified botulinum toxin at the buffered pH range of between 5 and 6 as recited in the instant

claims. This is critical because of what the state of the art taught at the time of the invention. See the above-identified teachings of Schantz *et al.* (*Perspect. Biol. Med.* 40 (3) Spring 317-327, 1997). Additionally, a review of the relevant art indicates that one cannot maintain stability of the purified botulinum toxin solution that is compatible for *in vivo* use, i.e., a diluted solution comprising nanogram concentrations of the purified toxin (i.e., therapeutic dose), **unless** another specific protein, such as, gelatin or human serum albumin, is added for protection. See first full paragraph in right column on page 83 of Schantz *et al.* (*Microbiol. Rev.* 56: 80-99, 1992, already of record). Similarly, Schantz and Sugiyama (*J. Agr. Food Chem.* 22: 26-30, 1974) taught that botulinum neurotoxin by itself 'loses toxicity *unless* it is held in the presence of some protein such as gelatin or the blood serum proteins' (see last part in left column in page 28) [Emphasis added]. Thus, the art clearly reflects unpredictability in maintaining the stability of a pharmaceutical botulinum toxin formulation meant for *in vivo* use in the absence of gelatin or human serum albumin. Instant claims, as presented currently, encompass a stabilized liquid pharmaceutical toxin formulation that is non-enabled, i.e., a stabilized liquid pharmaceutical toxin formulation comprising a therapeutic concentration of a purified botulinum toxin wherein the formulation is *not* required to comprise gelatin or human serum albumin. However, such a non-serum albumin- or non-gelatin-containing stabilized liquid pharmaceutical botulinum toxin formulation comprising a therapeutic concentration of a purified botulinum toxin, as claimed, is not enabled. Therefore, the full scope of the claims is not commensurate with the enabling disclosure. Furthermore, whether or not one can extrapolate the instant showing of stability in a pH 5.6 'succinate buffer' that contains 0.58% NaCl and 0.5 mg/ml of human serum albumin, to therapeutic concentrations of other botulinum toxin types is neither known nor established within the instant specification. A review of post-filing art indicates that those of skill in the art have not yet successfully showed that the stability features demonstrated with the BoNT-B or Myobloc™ liquid formulation are applicable or reproducible with botulinum toxins of other types, such as, type A, C1, C2, D, E, F and G (see Grethlein *et al. Pain Med.* 2: # 203, page 239, 2001, already of record). Given the art-known existence of 'structural and pharmacologic differences between the types' of botulinum toxin and a lack of definitive therapeutic equivalence between the toxins (see second half of page 81 of Moyer *et al. In*: *Therapy with Botulinum Toxin.* (Ed) J. Jankovic *et al.* Marcel Dekker, Inc.,

New York, pages 71-85, 1994), there is no predictability that 'a therapeutic concentration' of other types of botulinum toxin, such as, types A, C1, C2, D, E, F and G, when formulated as a liquid pharmaceutical formulation as recited in the instant claims would be capable of remaining stable at the recited temperature range for the recited duration of time. Therefore, the full scope of the claims is viewed as not being commensurate with the enabling disclosure. Due to the lack of specific disclosure and/or guidance, the lack of evidence or the lack of working examples enabling the full scope, the art-recognized unpredictability factor relevant to stability of the diluted purified botulinum toxin meant for *in vivo* use, the breadth of the instant claims, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the invention, as claimed. The ability to reproducibly practice the full scope of the claimed invention is well outside the realm of routine experimentation. The enablement (scope) provisions of 35 U.S.C. § 112, first paragraph, are not met.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

21) Claims 1-28 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1 and 16 are vague, indefinite and confusing in the limitations: 'stabilized liquid' (see line 1) and 'capable of being stable as a liquid'. How the term 'stabilized liquid' differs in scope from the 'liquid' that is 'capable of being stable' is not clear.

(b) Claims 7 and 20 are vague and indefinite because it is unclear how said 'buffered saline' can be selected from the group consisting of a 'buffer' such as phosphate buffer, phosphate-citrate buffer, and succinate buffer. Because of these inconsistent limitations, whether or not the limitation 'buffered saline' is synonymous with 'buffer' in terms of scope is not clear.

(c) Claims 4 and 18 are indefinite because these claims have improper antecedent basis in the limitation 'said buffered pH is'. Claims 4 and 18 depend from claims 1 and 16 respectively, which recite a 'buffered pH range', but not a 'buffered pH'.

(d) Claims 9 and 11-13 are indefinite and confusing in the limitation: 'toxin ...

present at a concentration'. Claims 9 and 11-13 depend directly or indirectly from claim 1, wherein the toxin 'concentration' is limited to 'a therapeutic concentration'. Therefore, with regard to the limitation 'toxin ... present at a concentration', the dependent claims 9 and 11-13 are improperly broadening in scope.

(e) Claims 22 and 24-26 are indefinite and confusing in the limitation: 'toxin ... present at a concentration'. Claims 22 and 24-26 depend directly or indirectly from claim 16, wherein the toxin 'concentration' is limited to 'a therapeutic concentration. Therefore, with regard to the limitation 'toxin ... present at a concentration', the dependent claims 22 and 24-26 are improperly broadening in scope.

(f) Claims 1 and 16 are vague in that these claims lack a preceding article in between the limitation 'of' and 'purified botulinum toxin' (see line 5).

(g) Claims 2-15 and 17-28, which depend directly or indirectly from claim 1 or 16, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

22) Claims 1-3, 5-8, 16, 17 and 19-21 are rejected under 35 U.S.C § 102(b) as being anticipated by Sacks *et al.* (*Applied Microbiology* 28: 374-382, 1974, already of record).

The limitation 'for therapeutic use in humans' in the base claims represents the intended use of the claimed product. The limitation in the dependent claims 7 and 20: 'said buffered saline is selected from the group consisting of ..... buffer .....' indicates that the term 'buffered saline' recited in the base claims is equivalent to each of the 'buffer' recited in the dependent claims. Therefore, the limitation 'buffered saline' is interpreted as being same as 'buffer' in this rejection. The phrase 'the formulation is .... stable .... degrees centigrade ...' in the instant claims is viewed as a functional limitation that does not define the formulation structurally. It is noted that instant claims do not place a dose/concentration limit to the recited 'therapeutic concentration suitable for use in humans'. It is noted that the term 'stable' is defined at lines 15-17 of page 6 of the specification as referring to retention of biological activity or potency by a biologically active substance, specifically botulinum toxin, over a defined or indefinite period of time. While the term

'stabilized .... formulation' does not appear to exist in the instant specification, the term 'stable' is not associated with, or limited to, or equated to a specific degree of retention of biological activity of a botulinum toxin, or a specific percentage of potency.

Sacks *et al.* taught a stable (i.e., stabilized) preparation of a purified *Clostridium botulinum* type E toxin contained in a pH 6.0 phosphate buffer that was stable for up to 1 year when stored at 4° C (see the last incomplete paragraph on page 379). The toxin was column-purified (see third full paragraph on pages 374, 376 and 379). The toxin that was purified at pH 6.0 from the culture filtrate by ion-exchange chromatography contained a lower concentration of the toxin (see paragraph bridging the two columns on page 380). Since the prior art buffer having a pH of 6.0 and Applicants' 'phosphate buffer' recited for example in claims 7 and 20, are one and the same, the prior art buffer is expected to necessarily have a pK in the range of pH 4.5-6.5. At least one of the non-peak fractions of the aged (i.e., stored) purified toxin eluted at pH 6.0 as depicted in Figure 13 of Sacks *et al.* is expected to contain the purified botulinum toxin in a therapeutic concentration range that is suitable for use in humans. Although Sacks *et al.* are silent about the functional limitations, i.e., the capability of being stable as a liquid when stored at the recited range of temperature for the recited period of time, this functional limitation is viewed as the unrecited technical effect of Sacks' stabilized liquid botulinum toxin formulation which formulation was already known in the prior art. Since the structural limitations are met by the prior art, the prior art stabilized liquid formulation is viewed as anticipating the instantly claimed product, and is expected to have the same functional properties as that of the Applicants' liquid formulation. There is sufficient overlap between the two compositions to reasonably conclude that Sacks' composition is one and the same as the Applicants' formulation. Since the Office does not have the facilities for examining and comparing Applicants' formulation with that of the prior art particularly with regard to the presence, in one of the non-peak columns fractions, of 'a therapeutic concentration suitable for use in humans', the burden is on Applicants to show a novel or unobvious difference between the claimed product and the product of the prior art . See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Claims 1-3, 5-8, 16, 17 and 19-21 are anticipated by Sacks *et al.*

23) Claims 1-8, 12-21 and 25-28 are rejected under 35 U.S.C § 102(b) as being anticipated by Schantz *et al.* (EP 0 593 176 A2, already of record) ('176).

The limitation 'for therapeutic use in humans' in the base claims represents the intended use of the claimed product. The limitation in the dependent claims 7 and 20: 'said buffered saline is selected from the group consisting of ..... buffer .....' indicates that the term 'buffered saline' recited in the base claims is equivalent to each of the 'buffer' recited in the dependent claims. Due to this inconsistency or indefiniteness, the limitation 'buffered saline' is interpreted in this rejection as being nothing more than a 'buffer'. The phrase 'the formulation is .... stable .... degrees centigrade ...' in the instant claims is viewed as a functional limitation that does not define the formulation structurally. The term 'stable' is defined at lines 15-17 of page 6 of the specification as referring to retention of biological activity or potency by a biologically active substance, specifically botulinum toxin, over a defined or indefinite period of time. While the term 'stabilized .... formulation' does not appear to exist in the instant specification, the term 'stable' is not associated with, limited to, or equated to a specific degree of retention of biological activity of a botulinum toxin, or a specific percentage of potency.

Schantz *et al.* ('176) taught a pharmaceutical composition comprising 100 U of crystalline type A botulinum toxin in a suitable buffer at a pH of about 5 to about pH 6.8 (which encompasses the recited pH range of between 5 and 6) and a stabilizing amount of a protein, such as, serum albumin (see page 2). Compositions comprising 100 or 1000 U of type A toxin (i.e., a therapeutic concentration) in sodium citrate buffer with pH 5.0, or sodium phosphate buffer with 5.5, both containing the excipient protein, bovine serum albumin, are taught in Table 1. Schantz *et al.* ('176) specifically taught that no detectable inactivation of type A crystalline toxin occurred during repeated freezing and thawing in pH 6.0 sodium succinate buffer, or pH 5.5 sodium citrate buffer (see last paragraph on page 3). A pharmaceutical composition comprising a dissolved botulinum toxin in a buffer solution of pH 5.0 and a protein stabilizer such as serum albumin is taught (see claims 5-8). Schantz *et al.* ('176) taught that full recovery of toxin activity is obtained when the pH is adjusted to 5.0 or 5.5 (see page 4). The crystalline botulinum type A toxin was prepared by the same procedure used for the manufacture of the toxin in the current

commercial product (see lines 18-19 on page 3), and therefore is viewed as inherently purified. The prior art buffer having a pH of 5.0 or 5.5 is expected to necessarily have a pK in the range of pH 4.5-6.5. Although Schantz *et al.* ('176) are silent about the functional limitation(s) on the capability of the formulation to be stable at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as unrecited technical effects of Schantz's ('176) liquid botulinum toxin formulation which formulation was already known in the prior art. Since the structural limitations are met by the prior art, the prior art liquid formulation is viewed as anticipating the instantly claimed product, and is expected to have the same functional properties as that of the Applicants' liquid formulation.

Claims 1-8, 12-21 and 25-28 are anticipated by Schantz *et al.* ('176).

Rejection(s) under 35 U.S.C § 103

24) Claims 1-9, 11, 16-22 and 24 are rejected under 35 U.S.C § 103(a) as being unpatentable over Schwarz (*Archiv. fur Lebensmittelhygiene* 30: 1-40, pp. 29-33, 1979 - original and translated documents, already of record) in view of Schantz *et al.* (*Perspect. Biol. Med.* 40 (3) Spring 317-327, 1997) (Schantz *et al.*, 1997).

The page number indicated below refers to the page number of the translated document.

The limitation in the dependent claims 7 and 20: 'wherein said buffered saline is selected from the group consisting of phosphate buffer .....' indicates that the term 'buffered saline' recited in the base claims encompasses each of the 'buffer' recited in the dependent claims. Therefore, the limitations 'buffered saline' and 'buffer' are interpreted in this rejection as having the same scope. The phrase 'the formulation is capable of being stable .... degrees centigrade ...' is viewed as a functional limitation that does not define the formulation structurally. The limitation in the dependent claims 10 and 23 'toxin ... is present in a ... complex' suggests that the 'purified botulinum toxin' as recited in the independent claims 1 and 16 is not free of proteins that are known to complex with botulinum toxin, for example, the nontoxic proteins, and therefore encompasses purified botulinum toxin complex.

Schwarz taught a stable (i.e., stabilized) liquid formulation comprising a purified serotype

B botulinum toxin and an acetate buffer solution having a pH in the range of 4.5 to 5.6, or a phosphate buffer at a pH of 6.0. The toxin was purified by ion exchange chromatography and was evaluated to be stable at 15°C. It is taught that at the pH range of 4.5 to 6.0 (which encompasses the recited pH range of between 5 and 6), a greater stability can be established at a storage temperature of 15°C than at the higher pH values (see abstract; page 2; Figures 1-3 and 6-8; page 9; and page 10, last paragraph). A formulation comprising a purified type B botulinum toxin dissolved in a citrate-phosphate buffer of pH 5.6 is taught (see page 3). The prior art buffer having a pH in the range of 4.5 to 5.6, or a pH of 5.6, is expected to necessarily have a pK in the range of pH 4.5-6.5. Although Schwarz is silent about the functional limitation(s) on stability at the recited temperature or range of temperature for the recited period of time, these functional limitations are viewed as the unrecited technical effects of Schwarz's stable liquid botulinum toxin pharmaceutical formulation which formulation was already known in the prior art.

Schwarz is silent about the concentration of the purified toxin in the disclosed formulation, or does not indicate the concentration to be a therapeutic concentration, including a concentration between 1000-5000 U/ml.

However, both the therapeutic use of a botulinum toxin in nanogram quantities, and the making of a formulation of a stabilized botulinum toxin for injection into patients by diluting milligram quantities of the toxin several thousands-fold, were well known in the art at the time of the invention. For instance, Schantz *et al.* (1997) taught the therapeutic use of a botulinum toxin in nanogram quantities (see second full paragraph on page 323). Schantz *et al.* (1997) expressly taught that the formulation of botulinum toxin and stabilization of the toxin for dispensing to physicians and subsequent injection into patients (i.e., for therapeutic use in human patients) required much care and research. Schantz *et al.* (1997) explicitly taught that the toxin be 'diluted' 10,000- to 20,000-fold from a milligram concentration to a concentration of 100 U per ml before being dispensed to physicians for subsequent injection into patients (see paragraph bridging pages 322 and 323).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to dilute Schwarz's purified botulinum toxin formulation using Schwarz's pH 5.6 buffer or Schwarz's buffer having a pH in the range of 4.5 to 5.6 in order to arrive at the

therapeutic concentration of the botulinum toxin as recited in the instant claims to produce the formulation of the instant invention with a reasonable expectation of success, since it was routine in the art to dilute milligram quantities of a botulinum toxin 10,000- to 20,000-fold to a therapeutic concentration of 100 U per ml in a formulation for subsequent injection into patients as expressly taught by Schantz *et al.* (1997). Given Schantz's (1997) explicit teaching, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing Schwarz's stable purified liquid botulinum toxin formulation in a concentration that is suitable for injection into patients. With regard to the specific concentration of type B botulinum toxin recited in claims 11 and 24, it should be noted that the determination or optimization of the toxin concentration in the formulation is well within the realm of routine experimentation. It has been held legally obvious and within the routine skill in the art to optimize a result effected variable. In the instant case, the toxin concentration in the formulation is clearly a result effected variable since the toxin is the active component of the formulation, and it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize this by increasing the toxin concentration in the prior art product by routine experimentation.

Claims 1-9, 11, 16-22 and 24 are *prima facie* obvious over the prior art of record.

Relevant Art

25) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Gimenez *et al.* (*Appl. Environ. Microbiol.* 53: 2827-2830, 1987) taught that purified type E botulinum toxin did not loose toxicity over a two month period, the longest storage time tested, when it was dialyzed against 0.03M phosphate buffer, pH 6.0, and stored at 4°C (see paragraph bridging pages 2829 and 2830).

- Sloop *et al.* (*Neurology* 48: 249-253, 1997) taught that reconstituted botulinum toxin type A does not lose potency in humans if refrozen or refrigerated (see entire document).

- The first full sentence on page 6 of the IDS document, i.e., the letter of 08/19/2005 submitted to the EPO, Munich by Nicholas Lee of Kilburn & Strode, states the

following:

A person skilled in the art would know that dilution of a formulation does not significantlyalter its pH.

- McMaster (US 6,146,902) taught the physiological saline to be 0.85% sodium chloride (see line 1 of column 5).

- Uvarova *et al.* (*Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii* 11: 42-46, 1980) taught a purified type F botulinum toxin solution contained in a pH 5.6 Na phosphate-phosphate buffer (see abstract).

Remarks

26) Claims 1-28 stand rejected.

27) Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

28) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The central Fax number for submission of amendments, responses and papers is (571) 273-8300.

29) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for

unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

November, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER